UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	8

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Kate Murashige (3) _____

(2) Lorraine Spector (4) _____

Date of Interview 2-17-99

Type: ☐ Telephonic ☐ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description: _____

Agreement ☐ was reached. ☐ was not reached.

Claim(s) discussed: Pending

Identification of prior art discussed: None

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: applicants proposed amendment addresses most issues. Applicants will consider amending claims to indicate variants which bind receptor, and to delete species containing drugs. A §132 showing species with ~~OS~~ or ~~OR~~ orientation would address scope issue.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

FORM PTOL-413 (REV.1-96)

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

A complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for response to Office action as specified in §§ 1.111,1.135. (35 U.S.C.132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s)) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Stimmary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

*U.S. GPO: 1996-404-496/40513

PATENT
Docket No. 295002005600
Client Reference CA0089

CERTIFICATE OF MAILING BY "FIRST CLASS MAIL"

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on February __, 1999.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Irving BOIME

Serial No.: 08/971,439

Filing Date: 17 November 1997

For: SINGLE-CHAIN BIFUNCTIONAL GLYCOPROTEIN HORMONES

Examiner: L. Spector

Group Art Unit: 1646

AMENDMENT UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is in response to an Office action herein mailed 2 December 1998, time for response to which was set to expire 2 March 1999. Claims 1-8 and 10-16 were examined and rejected. There was no rejection over the art; all rejections were based on 35 USC 112, first or second paragraph. It is believed that the following amendment and discussion are fully responsive to the grounds of rejection raised. Reconsideration and allowance are respectfully requested.

AMENDMENT

Please amend the claims as follows:

1. (Amended) A glycosylated or nonglycosylated protein having agonist and/or antagonist activity of the formula

β^1-(linker^1)$_m$-α-(linker^2)$_n$-β^2 (1); or

β^1-(linker^1)$_m$-β^2-(linker^2)$_n$-α (2); or

α-(linker^1)$_m$- β^1-(linker^2)$_n$-β^2 (3)

wherein each of β^1 and β^2 has the amino acid sequence of the β subunit of a vertebrate glycoprotein hormone which is selected from the group consisting of thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), leutinizing hormone (LH) and chorionic gonadotrophin (CG) or a variant thereof;

"α" designates the α subunit of a vertebrate glycoprotein hormone TSH, FSH, LH or CG or a variant thereof;

"linker" refers to a covalently linked moiety that spaces the β^1 and β^2 subunits at distances from the α subunit and from each other effective to retain said activity, and

each of m and n is independently 0 or 1;

wherein said agonist and/or antagonist activity is with respect to the receptor for which at least one of said β subunits is a ligand.

3. (Amended) The protein of claim 1 wherein at least one said linker moiety includes a drug to be targeted to the receptor for [the] at least one said glycoprotein hormone, or wherein at least one linker is CTP or a variant thereof.

5. (Amended) The protein of claim 1 wherein ~~the α subunit or [one or more] β subunits or [both]~~ one or more of any combination of α and β subunits ~~are~~ is modified by the insertion of a CTP unit or variant thereof into a noncritical region thereof and/or wherein said linker moiety includes a CTP unit or variant thereof.

6. (Amended) The protein of claim 1 wherein said variants contain 1-5 conservative amino acid substitutions as referred to the native forms or [are truncated forms] lack 1-5 amino acids at the N or C terminus of said sequences or both contain substitutions and lack 1-5 amino acids.

7. (Amended) A pharmaceutical composition which comprises the protein of claim 1 in admixture with a [suitable pharmaceutical] pharmaceutically acceptable excipient.

Please add the following claims:

--17. The protein of claim 1 which is of the formula
β^1-(linker^1)$_m$-α-(linker^2)$_n$-β^2 (1).

18. The protein of claim 17 wherein said β and α subunits are linked in head-to-tail configuration.

19. The protein of claim 18 wherein one of m and n is 0 and the other is 1 and wherein the linker is CTP.

20. The protein of claim 19 wherein m is 0, n is 1 and linker^2 is CTP.

21. The protein of claim 20 which is CGβ-α-CTP-FSHβ.--

REMARKS

The claims have been amended in response to some of the rejections under 35 USC 112, second paragraph, and further to clarify the invention. The claims have been renumbered in this response as the Office action indicates that claims 7-17 had been renumbered as 6-16.

Applicants appreciate the recognition that the claimed subject matter is free of the art. The invention lies in providing single-chain forms of the glycoprotein hormones TSH, FSH, LH

and CG with two β subunits included. Such constructions permit, but do not require, bifunctionality of the resulting single-chain proteins.

The Rejections under 35 USC 112, Second Paragraph

Claim 1 was objected to as indefinite on the basis that the receptor to which agonist or antagonist activity was exhibited was not clearly specified. This has been clarified in claim 1; since claims 11, 16 and 17 (or 11, 15 and 16, as renumbered) are dependent ultimately on claim 1, this explicit limitation is incorporated into these claims as well.

It is believed that the amendment to claim 3 obviates the putative unclarity in that claim.

With respect to claim 4's recitation of a position "proximal" to its C-terminus, it is believed unnecessary to insert the specific definition set forth in the specification into the claim. Page 9, line 26 explicitly sets forth an upper limit to "proximal." Thus, by definition, the word means within 10 amino acids of that terminus. The preferred embodiments, which are not claim limitations, are within 5 amino acids or at the terminus *per se*.

With respect to the asserted ambiguity in the definition of "partial CTP unit," reconsideration is requested. This ambiguity does not, in fact, exist; a "partial" CTP unit is not a "variant." It has its own definition which is specifically that set forth on page 10, lines 6-15. There is no limitation in this definition that only 10 amino acids can be deleted.

The asserted lack of clarity in claim 5 has been obviated by amendment.

Original claim 7 (now claim 6) has been clarified by amendment.

Former claim 8 (now claim 7) has been amended as kindly suggested by the Examiner.

The foregoing amendments and discussion are believed to obviate the rejections under 35 USC 112, second paragraph.

The Rejections under 35 USC 112, First Paragraph

Applicants appreciate the recognition that the pending claims are enabled for single-chain proteins of the formula β^1-(linker^1)$_m$-α-(linker^2)$_n$-β^2 wherein α, β^1, and β^2 represent α and β units of LH, FSH, TSH and CG. Applicants take this recognition at face value and thus assumes that claims of the scope of proposed new claim 17 and claims dependent thereon are free of this rejection.

Nevertheless, it is unclear to applicants why the Office appears to believe that only the embodiments of formula (1) as set forth above are enabled whereas the remaining embodiments of formulas (2) and (3) are not. Attention is called to page 12, beginning at line 19, which sets forth examples of alternative embodiments of formulas (2) and (3). Thus, the construction of such embodiments is clearly taught. What the Office appears to be questioning is whether or not there is proof that such embodiments will be effective as agonists or antagonists. Respectfully, the application teaches that these embodiments do have these activities. The Office has not pointed to any reason that these illustrative embodiments would not show such activities.

Turning, however, to the specific criticisms set forth in the basis for rejection, applicants respond as follows.

(a) The claims have been amended to recite specifically the 4 glycoprotein hormones intended all along. It is believed that the specification makes clear, beginning at page 4, line 23, that this is the intent.

(b) Applicants do not understand why there is an issue with respect to nonrecombinantly produced proteins. Certainly it is well known that proteins of any arbitrary length can be synthesized using commercially available solid-phase technology, as well as using a number of well known solution-phase systems. There is no necessity for using DNA technology to construct the proteins of the invention, although in many cases this is the most convenient approach. It is specifically noted on page 17, lines 14-24, that nonrecombinant methods can be used to synthesize these proteins, although this would be readily apparent to the skilled artisan. Clearly, however, the recombinant approach cannot be used if nongene-encoded amino acids are included in the proteins or if the linkers are not themselves amino acid sequences or if the subunits are linked in head-to-head or tail-to-tail configuration. This is set forth in some detail beginning at page 5, line 20-page 6, line 5. This paragraph merely alludes to what the skilled artisan would certainly know, that methods to synthesize nonfusion proteins of this type are well within ordinary skill. See also page 17, lines 14-24 cited above. Surely the Office does not question that such embodiments could be made. The text of the rejection, however, implies that the basis is other than failure to teach how to make, but rather how to select the appropriate components, in particular, the linker. This is discussed further in response to paragraph (d).

(c) The Office then questions the question of the arrangement of the subunits on the basis that the working example is of the sequence β-α-β and has been demonstrated to be

operable. The Office then advances several theories, not proposed by applicants, of why it is that the illustrative successful embodiment is, indeed, successful. It is unclear to applicants why these theories are relevant. If one of these options could be chosen, would it shed any light on whether β-β-α or α-β-β would work? The nexus of these theories and asserted unworkability of alternative configurations is not clear to applicants.

(d) Applicants agree with the point of view expressed by the Examiner that the nature of the linker is relevant to the operability of the claimed proteins. Applicants do not agree, however, that the selection of suitable linkers would require undue experimentation. As indicated in the working example, operable embodiments may not involve any linkers at all. It is well within ordinary skill to select a linker of appropriate functionality and hydrophilicity/hydrophobicity. This is discussed on page 12, lines 4-16. It is believed that this paragraph provides adequate guidance. The characteristics required by the linker are set forth in that paragraph. Similarly, as the Examiner kindly recognizes, the types of drugs that may be included are set forth on page 13, lines 12-22. A wide variety of such drugs is adaptable to the invention, and the choice depends, of course, on the purpose to be served in a particular instance by the construct.

Applicants can only agree enthusiastically that the ordinary artisan would be able to suggest possible linkers which would be expected to be neutral in effect; the functions proposed by the specification for the linker would also be within ordinary skill; it would not be possible for the specification to enumerate every possible disease indication or other condition intended to be targeted by the constructs of the invention.

As to the argument that it may not be possible in some cases to provide a particular drug within the context of the invention proteins, it is not believed that this results in a valid conclusion that the claims are of improper scope. Clearly, many drugs are susceptible of successful incorporation and function. As the Examiner has correctly recognized, there is no suggestion in the art to provide drugs in this context. Applicants should not be deprived of this concept based on speculation that it may not be applicable in each and every instance.

(e) With respect to truncated forms, it will be noted that former claim 7 (now claim 6) has been amended to specify deletions of only 1-5 amino acids at the N or C terminus. Thus, the issue relates only to variants. While the Examiner may be correct that the number of possible nonfunctional variants of each individual subunit would vastly outnumber functional variants

(although this may not, in fact, be true), this is not the issue. As the Examiner recognized, the specification sets forth a review of the knowledge in the art, which is extensive, as to what does and does not make a successful variant. Thus, the ordinary practitioner would not find it necessary to explore the success or failure with respect to all *possible* variants; sufficient guidance is provided by the art to focus the attention of the artisan on variants that would, indeed, be operable. The criticism that "noncritical" regions may be critical to obtaining the proper three-dimensional configuration of the protein is believed an error since the configuration of the protein would be critical in its heterodimeric state as well. The region would not be identified as "noncritical" based on the proper art if were thus essential.

(f) Applicants appreciate the acknowledgment that the specification is enabling of pharmaceutical compositions comprising proteins which act as agonists or antagonists of LH, CG, TSH or FSH. Applicants do not understand the criticism with respect to pharmaceutical compositions wherein the linker comprises a drug. Of course, the manner of using such compositions will depend on the nature of the drug; because one endeavoring to target a particular drug (of his or her own choosing) to a receptor for a particular glycoprotein hormone would presumably have some idea of why he or she wanted to use the drug in the first place, this would clearly be within the skill of one putting the invention into practice.

In view of the foregoing, it is believed that the rejection under 35 USC 112 may properly be withdrawn.

Conclusion

The claims have been amended in response to criticisms of lack of clarity. Further, it is believed that the invention as claimed, for the reasons stated above, is claimed in a manner consistent with 35 USC 112, first paragraph. There is no art rejection. Thus, it is respectfully submitted that claims 1-8 and 10-21 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952** referencing docket no. 295002005600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: February __, 1999

By: _____

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